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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,831	09/22/2006	Toshihiro Akaike	69719.000003	3234

21967 7590 05/27/2010

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
05/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,831	AKAIKE ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-20* is/are pending in the application.

4a) Of the above claim(s) *2 and 11-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/3/2010 has been entered.

Claim Status

Claims 1-9 and 11-20 are pending. Claim 10 is cancelled. Claims 2 and 11-18 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1, 3-9 and 19-20 are under current examination.

Priority

This application claims benefit as a 371 of a National Stage of PCT/JP05/06006, filed 23 March 2005. This application claims benefit as a foreign application JAPAN 2004-085393, filed 3/23/2004. The instant application has been granted the benefit date, 1 April 2004, from foreign application JAPAN 2004-085393, filed 3/23/2004.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 3 May 2010 consisting of 1 sheet is/are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

RESPONSE TO ARGUMENTS

35 USC § 103

The rejection of claims 1, 3-9 and 18-19 under 35 USC 103(a) as being obvious over Nagaoka et al (Biotechnology Letters, 2002; 24: 1857-1862) [known hereinafter as Nagaoka1] and as evidenced by Nagaoka et al. (Cell Structure and Function, 2003; 28(4): 327, IP-53) [known hereinafter as Nagaoka2] is withdrawn in response to the applicants arguments and/or claim amendments.

The applicant's arguments and claim amendments have been fully considered and are persuasive. The applicant has amended the claims to introduce the limitation, "which exhibit normal karyotype." The applicant has argued that the Nagaoka references do not teach or suggest a method of culturing pluripotent stem cells which exhibit normal karyotype. The examiner accepts these claim amendments and arguments. The examiner concludes that the addition of another secondary reference would strengthen the *prima facie* case for using the method disclosed by Nagaoka for

culturing normal karyotype stem cells. Therefore, the examiner will withdraw the pending rejection in favor of the new grounds of rejection below.

Therefore, the examiner hereby withdraws the rejection of claims 1, 3-9 and 18-19 under 35 USC 103(a) as being obvious over Nagaoka1 et al and Nagaoka2.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-9 and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagaoka et al (Biotechnology Letters, 2002; 24: 1857-1862) [known hereinafter as Nagaoka1] and in view of Nagaoka et al. (Cell Structure and Function, 2003; 28(4): 327, IP-53) [known hereinafter as Nagaoka2] and further in view of Alonso et al. (Int. J. Dev. Biol. 1991; 389-397).

Claim 1 is directed to a method for augmenting the proliferation potency of pluripotent stem cells, comprising growing said pluripotent stem cells in a dispersed state while maintaining their undifferentiated state and pluripotency, in a liquid medium and culturing vessel including immobilize or coated on a substrate solid phase surface a molecule which is adhesive to said pluripotent stem cells, without using feeder cells. Nagaoka1 teach growing F9 teratocarcinoma cells in a liquid medium and in a culturing vessel having a E-cadherin-IgG Fc coated surface (page 1860, col.1). F9 carcinoma teratocarcinoma cells are an undifferentiated cell line derived from a mouse embryonal carcinoma that is frequently used as a model for studying differentiation and pluripotency. In Nagaoka1, the F9 cells were used as a control and were not the primary subject of interest in the Nagaoka1. However, Nagaoka2 indicates that F9 mouse teratocarcinoma-derived embryonal carcinoma cells cultured on immobilized E-

cad-Fc [fusion protein of E-cadherin extracellular domain and Immunoglobulin G (IgG) Fc region] remained undifferentiated. No feeder cells were used in either reference. Since the F9 cells in Nagaoka1 were cultured under identical conditions as in Nagaoka2, the examiner asserts that Nagaoka1 describes all the limitations of claim 1, with the exception that the specific cells cultured are not actual stem cells.

However, Alonso et al. suggest that F9 embryonal carcinoma cell line can be used as a substitute for embryonic stem cells, when studying differentiation. See in particular, page 390, paragraphs 2 & 4.

Claim 3 is directed to the method of claim 1, wherein the molecule which is adhesive to said pluripotent stem cells is either a molecule that is expressed by said pluripotent stem cells or a molecule that is structurally homologous with said molecule and has homophilic binding ability with said pluripotent stem cells. Nagaoka1 describes the E-cad-Fc as creating a homophilic interaction of E-cadherins (abstract).

Claim 4 is directed to the method of claim 3, wherein the molecule which is adhesive to said pluripotent stem cells is a molecule belonging to the cadherin family. The molecule, E-cadherin, is a part of the cadherin family.

Claim 5 is directed to the method of claim 4, wherein said molecule belonging to the cadherin family is E-cadherin, or a molecule which has structural homology with said molecule, which comprises the EC1 domain and one or more domains from among the EC2 domain, EC3 domain, EC4 domain and EC5 domain and which has homophilic binding ability with said pluripotent stem cells. The molecule, E-cadherin, is a part of

the cadherin family. Nagaoka1 describes the E-cad-Fc as creating a homophilic interaction of E-cadherins (abstract).

Claim 6 is directed to the method of claim 5, wherein said E-cadherin is obtained from a mammal. The extracellular domain of E-cadherin used in the fusion protein is from mouse E-cadherin (Nagaoka1, Figure 1, page 1858).

Claim 7 is directed to the method of claim 6, wherein said E-cadherin is obtained from a human or mouse. The extracellular domain of E-cadherin used in the fusion protein is from mouse E-cadherin (Nagaoka1, Figure 1, page 1858).

Claim 8 is directed to the method of claim 1, wherein the molecule which is adhesive to said pluripotent stem cells is fused with an immunoglobulin Fc region and is immobilized on said substrate solid phase surface via said Fc region. Nagaoka1 teach a fusion protein comprising E-cadherin extracellular domain and Immunoglobulin G (IgG) Fc region. Nagaoka1 teach "we have applied an engineered protein of E-cadherin extracellular domain and immunoglobulin G (IgG) Fc region because Fc region has the potentiality to stably adsorb to a plastic surface such as polystyrene and dimerize via the hinge region." (page 1857, col.2).

Claim 9 is directed to the method of claim 1, wherein said pluripotent stem cells are mammalian embryonic stem cells (ES cells) or embryonic germ cells (EG cells). The specification indicates "'Pluripotent stem cells' are defined as cells capable of prolonged or virtually indefinite proliferation in vitro while retaining their undifferentiated state, exhibiting normal karyotype (chromosomes) and having the capacity to differentiate into all cell types of the three germ layers (ectoderm, mesoderm and

endoderm) under the appropriate conditions." (page 2, lines 29-35). The F9 mouse teratocarcinoma-derived embryonal carcinoma cells of Nakaoka have a polyoma-based plasmid that persists as an episome, but have a normal karyotype. These cells are capable of differentiation into virtually all cell types of the body. Alonso et al. teach that "EC cells are the stem cells of teratocarcinomas" (page 390, parag.2), thereby suggesting that embryonic stem cells and F9 can be substituted for each other in various culturing methods.

Claim 19 is directed to the method of claim 1, wherein the molecule which is adhesive to said pluripotent stem cells is E-cadherin obtained from a human or mouse and said pluripotent stem cells are mammalian embryonic stem cells (ES cells). Nagaoka teach the method of claim 1 as described above in the 35 USC 102(b) rejection. Nagaoka do not explicitly teach culturing embryonic stem cells. However, Nagaoka2 teach that the E-cadherin-Fc fusion protein could be used to study embryonic development. This is suggestive of culturing mammalian embryonic stem cells in the method of claim 1, as culturing embryonic stem cells would provide the suitable material for studies of mammalian development. As the cells used in the Nagaoka are murine cells, therefore mammalian embryonic stem cells are suggested. Furthermore, Nagaoka teaches that the E-cadherin domain of the E-cad-Fc fusion protein is from a mouse (Fig.1)

Claim 20 is directed to the method of claim 19, wherein the E-cadherin is fused with an immunoglobulin region and is immobilized on said substrate solid surface via

said Fc region. Nagaoka teaches that the Fc region has the potentiality to stably adsorb to a plastic surface (page 1857, col.2).

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to culture mammalian embryonic stem cells using the system of Nagaoka.

The person of ordinary skill in the art would have been motivated to make that modification to culture mammalian embryonic stem cells using the system of Nagaoka because Nagaoka2 suggests that the E-cadherin-Fc fusion protein could be used to study embryonic development and a suitable material for studies of mammalian development would be mammalian embryonic stem cells. Furthermore, Alonso et al. suggest that "EC cells are the stem cells of teratocarcinomas" (page 390, parag.2), thereby suggesting that embryonic stem cells and F9 can be substituted for each other in various culturing methods.

An artisan would have expected success, because Nagaoka demonstrates a method of growing pluripotent cells such as F9 mouse teratocarcinoma-derived and embryonal carcinoma cells are known to be useful as a model of embryonic development and are models for embryonic stem cells.

Therefore the method as suggested by Nagaoka et al. in view of Alonso et al. would have been *prima facie* obvious over the method of the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 9 are rejected under 35 U.S.C. 102(b) as being anticipate by Xu et al. (Nature Biotechnology. October 2001; 19: 971-974).

Claim 1 is directed to a method for growing pluripotent stem cells which exhibit a normal karyotype comprising growing said pluripotent stem cells in a dispersed state while maintaining their undifferentiated state and pluripotency, in a liquid medium and culturing vessel including immobilize or coated on a substrate solid phase surface a molecule which is adhesive to said pluripotent stem cells, without using feeder cells. Xu et al. teach feeder-free growth of undifferentiated human embryonic stem cells on matrigel or laminin in conditioned medium (title, abstract). Xu et al. teach the hES cells in feeder-free conditions maintained a normal karyotype (abstract). Xu et al. teach the cells are dissociated prior to plating on coated substrate solid phase surface (experimental protocol).

Claim 3 is directed to the method of claim 1, wherein the molecule which is adhesive to said pluripotent stem cells is either a molecule that is expressed by said pluripotent stem cells or a molecule that is structurally homologous with said molecule and has homophilic binding ability with said pluripotent stem cells. Embryonic stem

cells have a laminin receptor which would be homophilic with the laminin coated on the culture plate. Furthermore, embryonic stem cells express laminin.

Claim 9 is directed to the method of claim 1, wherein said pluripotent stem cells are mammalian embryonic stem cells (ES cells) or embryonic germ cells (EG cells). Xu et al. teach human embryonic stem cells.

Accordingly, Xu et al. anticipated the instant claims.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Primary Examiner, Art Unit 1633